25th Meeting of the Transmissible Spongiform Encephalopathies Advisory Committee
Food and Drug Administration
Silver Spring, Maryland
June 1, 2015

Issue Summary

I. Topic

Reconsideration of FDA's geographically based donor deferral policies to reduce the risk of transfusion-transmitted variant Creutzfeldt-Jakob disease

II. Issue

In the context of other possible risk mitigation strategies that will be discussed, FDA seeks advice from the Transmissible Spongiform Encephalopathies Advisory Committee whether narrowing of the geographically based donor deferrals for risk of vCJD is appropriate at this time based on the results of (a) a new FDA-developed quantitative assessment model for vCJD global geographic risk; and (b) the estimated additive risk reduction achieved by the current 95% voluntary implementation of leukocyte reduction (LR) for red blood cells (RBC).

III. Introduction

In 1987, FDA, concerned by experimental studies showing that infectivity was present in blood of animals with transmissible spongiform encephalopathies (TSEs), issued the first of a series of precautionary recommendations (1) intended to reduce the risk that recipients would be transfused with blood components from donors incubating Creutzfeldt-Jakob disease (CJD). Reports in 1996 of a new "variant" form of CJD (vCJD) attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) prompted FDA, starting in 1999, to issue several revised guidances intended to reduce the theoretical risk of transfusion-transmitted vCJD (TTvCJD) by recommending that blood establishments defer donors resident in certain countries where the risk of dietary exposure to the BSE agent was higher than that in the US. The UK first reported a presumptive clinical case of TTvCJD in 2003, followed by two other clinical cases and

two preclinical or subclinical infections, one attributed to a transfusion of RBC and the other to treatment with a plasma derivative.

Accumulating evidence suggests that cases of BSE in cattle and vCJD in humans have declined markedly in recent years, both in the UK and worldwide. Especially encouraging is the fact that no new cases of TTvCJD have been recognized in the UK since 2007. This is possibly related to a shrinking number of infected donors in the UK because of aging of the population exposed to the BSE agent (fewer donating blood), due to the introduction of universal leukoreduction (LR) in the UK in 1999, or both. No case of TTvCJD has been reported from any other country, including the US.

The geographic deferral policies implemented by US blood establishments are likely to have greatly reduced the risk of TTvCJD. However, they have also eliminated a substantial number of otherwise suitable blood donors, most of whom are unlikely to be incubating vCJD. The geographic deferral policies have also complicated the donor questionnaire, increased the number of post-donation biological deviation reports, and occasioned considerable distress among some dedicated blood donors who are deferred.

The declining BSE and vCJD epidemics worldwide combined with likely beneficial effect of LR in preventing TTvCJD (as evidenced in the UK and possibly in other countries) has encouraged the FDA, which is committed to revisiting its blood safety policies at reasonable intervals, to consider the possibility of modifying the currently recommended geographic deferral policies. As before, when considering such changes to its vCJD-related donor deferral policies, FDA asks the TSE Advisory Committee (TSEAC) for advice. To assist the FDA and TSEAC in addressing this issue, FDA has developed a new quantitative risk assessment tool (described in Appendix A) and suggested a possible modification to donor deferral policy based on results of the risk assessment.

FDA's risk assessment model ranks the risk of vCJD in different countries. The risk contributions of individual countries were estimated based on either the observed ("attributed") vCJD case rate of the country or a rate "imputed" from the probable exposure of the population to the BSE agent in beef products, and the potential person-year exposure in that country by US donors (US travelers in the country and immigrants to the US from the country). FDA further used the model to evaluate both risk reduction and donor loss resulting from the current donor deferral policy compared with an alternative deferral option. FDA also evaluated a potential additional reduction in risk afforded by LR of red blood cells (RBC).

The model estimated that current geographic donor deferrals for vCJD risk combined with voluntary implementation of LR by blood centers—accounting for approximately

95% of all RBC transfusions in the US—has already reduced the risk of TTvCJD via RBC by about 90%. Exposures in the UK, Ireland and France—three countries with the highest attributed vCJD case rates—together contribute approximately 95% of total vCJD risk from worldwide exposure to BSE in US donors.

FDA proposes, for consideration, an alternative donor deferral option that defers individuals who had history of accumulative time spent in UK of three months or more during the period 1980-1996 (same as current policy) and donors who spent time in France or Ireland of five years or more during the period 1980-2001. This option would simplify the donor screening process and allow more donors to donate. The model results showed that a level of blood safety similar to that from current policies would be maintained under the new deferral option. The model estimated that the added risk reduction achieved by implementing universal LR (not required by the FDA) would be small compared with risk reduction already afforded by the current voluntary LR of 95% of RBC in the US.

IV. Background

Dietary exposure to beef products from cattle infected with the BSE agent is the likely cause of primary variant Creutzfeldt-Jakob disease (vCJD) in humans. vCJD is a fatal neurodegenerative disease with long asymptomatic incubation periods and with no validated test to identify affected individuals prior to onset of overt illness. vCJD-infected individuals accumulate abnormally folded prion protein (PrP^{TSE}) in brain and lymphoid tissues. PrP^{TSE} is usually associated with infectivity and is widely used as the biochemical marker for infectivity. As of March 2015, a total of 228 vCJD cases have been recognized worldwide, of which 177 cases were reported in the UK (plus 4 cases in Republic of Ireland) and 27 cases in France (2).

BSE is a transmissible spongiform encephalopathy (TSE) infection mainly affecting cattle. BSE was first recognized in the UK in 1986 (3) and later spread to other countries, mostly in Europe, probably through UK exports of bovine meat-and-bone meal that contaminated cattle feed (4). vCJD was itself mainly spread by exporting carcass beef and beef products for human consumption from the UK (5). Highly effective anti-BSE/vCJD measures were implemented in the UK by the end of 1996 and somewhat later in other countries, presumably leading to the decline in BSE and vCJD cases. However, BSE has not been eradicated, and a few new cases are still reported each year (6). In addition, more recently, atypical cases of BSE have been reported with neuropathological features and PrP^{TSE} biochemical patterns somewhat different from those observed in "classical" BSE (7). Some authorities consider atypical BSE to be a form of

spontaneously occurring BSE not acquired from contaminated cattle feed. This hypothesis remains to be rigorously confirmed, and the FDA, as well as the World Organisation for Animal Health (OIE), does not currently discriminate between the two forms of BSE regarding the threat to health of humans and animals.

There have been only four cases of BSE reported in the US, three in US-born cattle and one in a cow born in Canada (8, 9). Thus, the risk that blood donors in the US may have acquired vCJD infection through consumption of US beef is thought to be negligible. Consistent with this conclusion, none of the four cases of vCJD recognized in the US appears likely to have resulted from a US exposure: two cases occurred in long-time residents of the UK, a third occurred in a recent immigrant from the Kingdom of Saudi Arabia (KSA) (10, 11), and a fourth US vCJD case was in an individual whose history of residence suggested that Kuwait, Lebanon and Russia were the most likely countries of exposure (8). Canadian authorities have similarly attributed two cases of vCJD recognized there as resulting from infection acquired outside the country (12).

vCJD infectivity is present in the blood of affected individuals, persisting during the asymptomatic phase of disease for at least 3.5 years prior to onset of overt illness. Donors, unknowingly infected with vCJD and healthy at the time of donation may donate blood that transmitted vCJD to recipients. A total of three symptomatic vCJD infections (13-15) and one asymptomatic infection were probably transmitted by non-leukocyte reduced RBC transfusions in the UK (16); one additional UK case of asymptomatic infection was linked to treatment with plasma-derived Factor VIII (17). As mentioned, reports of clinical vCJD cases are in decline worldwide, but the true latent vCJD prevalence in the UK population is still unknown. Immunohistochemical detection of PrP^{TSE} in a number of samples among thousands of archived appendix specimens suggested a possible high prevalence of latent vCJD infection—1:2,000—in the UK population, generally consistent with results from smaller surveys conducted previously (18-20). A major limitation of all these tissue surveys is lack of an adequate number of negative control samples to assess the false positive rate for immunohistochemical detection of PrP^{TSE}. A new survey of probable low-risk appendix samples is currently under way in the UK to address that problem. Should a substantial number of persons with PrP^{TSE}-positive appendices prove to have latent vCJD infections with the agent in blood, implications for transfusion safety would be significant (21). Absent scientific information to clarify this issue, FDA's donor deferral policies are based on the assumption that asymptomatically infected donors might transmit vCJD by transfusion.

Transfusion-Transmitted vCJD mitigation measures

Measures to mitigate the risk of TTvCJD have been discussed at various TSEAC meetings (22, 23). In addition to donor deferral policies already in place, approaches considered were assays to detect PrP^{TSE} in blood of potential donors and removal of infectivity from blood by LR filters and by devices that selectively retain PrP.

Donor screening tests

FDA recognizes the potential value that practical blood screening tests would have to detect and defer latently infected donors of blood, plasma and tissues during the asymptomatic incubation periods of vCJD. FDA continues to encourage the development and validation of such tests; several developers of candidate tests presented interim progress reports to open meetings of TSEAC in 2006 (22), and the committee offered advice regarding possible pathways that might lead to FDA licensure of validated donor screening tests. However, the number of laboratories developing candidate assays has been declining during the years since that review, and only a few assays remain under evaluation: the UK Medical Research Council (MRC) Prion Unit has reported a candidate test (24). Two in vitro conversion assays, Real Time-Quaking-Inducing Conversion (RT-QuIC), recently modified (25, 26); a Protein Misfolding Cyclic Amplification (PMCA) assay was described earlier (27, 28). The UK National Institute of Biological Standards and Controls (NIBSC) has proposed an algorithm to evaluate performance of antemortem assays using TSE-related reference materials. At the moment, no blood test has been validated by NIBSC as suitable for donor screening. The MRC assay reportedly achieved 100% specificity and about 70% sensitivity in tests with a small number of blood samples from patients diagnosed with vCJD (29; http://www.nibsc.org/science_and_research/virology/cjd_resource_centre/cjd_test_evaluation.aspx).

Prion-protein removal filters

Three TSE infectivity reduction devices have targeted the RBC component of Whole Blood. Two devices are LR filters that reduced the content of TSE infectivity in pilot studies (30-32). A third filter has been applied to previously leukoreduced RBC; the active component is a proprietary ligand claimed to adsorb both brain-derived and endogenous TSE infectivity from blood (33). That filter was also evaluated with BSE-infected macaque blood; interim results showed no transmission from treatment blood to three monkeys observed for five to six years after transfusion (34). The same filter was evaluated in the UK for its safety and impact on component quality (35, 36). A committee advisory to UK authorities on the safety of blood, tissues and organs (SaBTO) once recommended “prion filtration” of blood intended for certain recipients (37), but the procedure has not been implemented in the UK, and SaBTO has not recommended it recently (38). Irish authorities also conducted a health technology assessment of prion

filtration of blood and, in 2011, advised against implementation following a cost-benefit analysis (39). To our knowledge, no prion protein removal device is currently in clinical use for transfusible blood components, although a resin containing prion-protein affinity ligand was incorporated into the production of a commercial preparation of plasma for further manufacture (40).

Leukocyte reduction filtration

In 1999, the UK implemented universal LR of all cellular components. This strategy was based on results of early animal studies demonstrating that buffy coats from blood of animals with TSEs contained the highest concentrations of infectivity in blood (41, 42). A LR filter removed considerable infectivity from blood of hamsters experimentally infected with rodent-adapted scrapie agent, although a substantial amount of infectivity remained detectable in plasma (43). Similar results were obtained when whole leukoreduced units of blood from sheep infected with scrapie or BSE agents were transfused into naïve sheep (44). In short, LR of blood from animals with experimental TSEs consistently failed to remove infectivity completely from components.

However, experience in the UK with universal LR of blood from asymptomatic donors during the past 16 years has been far more encouraging than animal studies would have predicted; all four TTvCJD infections reported in the UK to date have been from a cohort of 27 persons transfused with non-leukoreduced RBC from donors who later became ill with vCJD, while none of 25 transfusions of leukoreduced RBC from vCJD-infected donors have transmitted vCJD to recipients (45). These compelling data indicate that LR reduced the risk of TTvCJD to recipients. This apparent inconsistency between results from animal studies and experience with human recipients may have resulted from the relative small amount of infectivity present in blood of humans incubating vCJD compared to higher concentrations estimated in TSE-infected rodent blood (46).

In addition to reducing the risk of TTvCJD, LR also provides other medical benefits. Pre-storage removal of nucleated cells eliminates a major portion of the proinflammatory and prothrombotic mediators released into blood by leukocytes (47-51). Adverse effects attributed to leukocytes in transfused blood components include febrile non-hemolytic transfusion reactions, graft-versus-host-disease, alloimmunization, and immunomodulation (52), and transmission of cell-associated blood-borne pathogens (cytomegalovirus, human T-cell lymphotropic viruses, and possibly others)—all reported to be ameliorated by LR. The summary in Appendix B describes benefits and limitations of LR in detail.

History of current FDA blood donor deferral policies and their rationale

FDA has conducted a number of risk assessments (models) to estimate the risk of TTvCJD to US blood recipients based on an assumption that the risk to the US blood supply comes mainly from US donors potentially exposed to the BSE agent during travel or residence in the UK and, to a lesser extent, in other countries with increased BSE risk. FDA concluded that, recognizing the uncertainties for certain critical model inputs, the probable risk to blood recipients is small (21).

In 1999, consistent with advice from the TSEAC, FDA recommended precautionary deferrals of blood and plasma donors who had traveled or lived for six months or longer in the UK during a period extending from the presumed start of the BSE outbreak in 1980 until the end of 1996, when the UK had fully implemented a range of measures to protect animal feed and human food from contamination with the BSE agent (53). In 2002, FDA recommended enhancing the vCJD geographical donor deferral policy by reducing the time that an otherwise suitable blood donor might have spent in the UK from six to three months (54). FDA also recommended deferring donors who had spent five or more years cumulatively in France or other countries in Europe listed by the USDA as either having had BSE or having a significant risk of BSE, and donors with a history of blood transfusion in the UK (or injections of beef insulin from the UK) from 1980 onwards. FDA also recommended deferral of donors based on time and duration of exposure at military bases in Europe during periods in which commissaries were supplied with beef products from the UK. In 2010, FDA issued a revised guidance document to include deferral of blood donors transfused in France since 1980 (23). These FDA recommendations have been periodically revisited as needed, taking into account current scientific information, with the goal of improving blood safety while maintaining an adequate blood supply. In 2011, FDA convened a TSEAC meeting to discuss the significance of a new vCJD case reported from Canada in an individual with a long history of residence in KSA. The committee recommended deferral for residence in KSA (55, 56) similar to that for most countries of Western Europe. FDA has, since that time, considered the 2011TSEAC recommendation as part of a broader re-evaluation of all vCJD-related deferral policies for donors of blood and tissues. To that end, FDA conducted a global vCJD risk assessment that reviews the probable prevalence of vCJD and BSE infections worldwide at this time, taking into consideration the fact that surveillance efforts show both diseases to be in marked decline. FDA believes that it is now appropriate to revisit FDA's vCJD-related donor deferral policies to ensure that they continue to protect the public from the risk of TTvCJD while minimizing unnecessary deferrals of otherwise suitable blood donors. The global geographic vCJD risk assessment model is intended to assist in the review of FDA policies.

FDA's vCJD Global Geographic Risk Assessment Model

A. Assessment of vCJD Risk Based on Geographic Exposure in US Donors

Overview of the FDA Geographic Risk Assessment Model

FDA developed a computer-based model to rank the risk of vCJD for donors resident in different countries. The risk contribution of an individual country was calculated based on two major factors: (1) vCJD case rate of the country (actual or imputed) as an indicator of the individual risk of exposure to vCJD in a country, and (2) the potential person-year exposure of US donors who were in in that country. The model includes three modules (Figure 1). Module 1 calculates vCJD case rate of individual countries; module 2 calculates the person-year exposure of US donors in a vCJD risk country based on US data on travel and immigration and the blood donation rate of US citizens; and module 3 calculates and ranks the risk contribution of individual country. For details of the model see Appendix A.

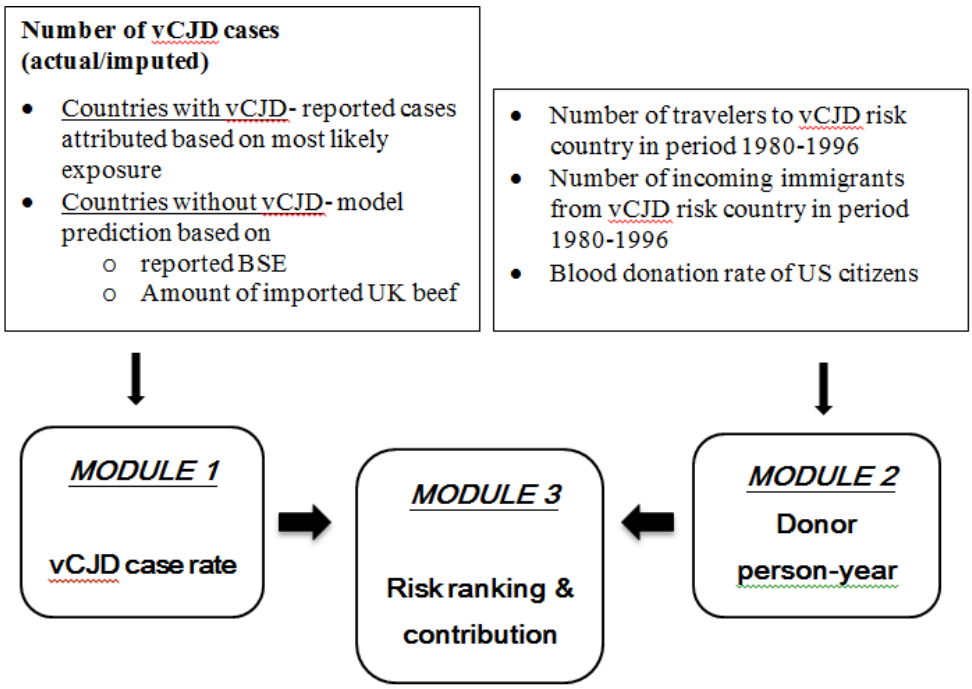

Figure 1. Model diagram for geographic risk assessment model

Estimation of country-specific vCJD case rates

vCJD case rates determined based on attributed actual vCJD cases

For a country with any attributed vCJD case, the vCJD case rate was calculated based on the number of those attributed cases and the country's population.

Major input data

Reported vCJD cases: UK National CJD Research and Surveillance Unit (2).

Major assumption

Most cases (with a few exceptions) were assigned to the countries where the cases were reported. We accepted the UK convention of assigning a case to the UK when an individual had resided there for more than six months during the period 1980-1996. The other exceptions were those vCJD cases attributed to non-reporting countries by US or Canadian authorities because of the individual's history of residence at the time of most probable infection based on a plausible incubation period (see Appendix A for details).

vCJD case rate predicted by the model based on BSE risk for the countries without recognized vCJD cases

Countries with reported cases of BSE or records of importing beef from the UK during the BSE risk period 1980-1996 may have potential vCJD risk, even if vCJD cases have not been reported in those countries. vCJD may have not occurred because of low vCJD case rates or small populations in these countries, or the vCJD cases may have been underreported because of imperfect diagnoses of the disease or ineffective surveillance systems. Individuals with vCJD may also have died of other causes before vCJD became symptomatic. FDA developed a computational BSE model to predict (impute) vCJD case rates for those countries without attributed vCJD cases based on reported BSE cases and amounts of beef imported from the UK during the period 1980-1996.

Major input data

Reported BSE cases: World Organisation for Animal Health (OIE), (6).

Amount of beef imported from UK from 1988 to 1996: Eurostat (57)

Major assumptions

The number of vCJD cases in a country directly correlates with total BSE exposure of the population.

There are two dietary sources for BSE exposure:

- BSE-infected domestic beef
- Beef imported from the UK during the period 1980-1996

Imputed vCJD case rates

The model imputed country-specific vCJD case rates by the following steps (see Appendix A for a more detailed description of the imputation procedure):

We calculated country-specific average annual importation of UK beef based on data for the years 1988 to 1996 and extrapolated to the entire BSE risk period 1980-1996. We calculated the total amount of UK beef exported from the UK to a country during the period 1980-1996, and converted that value into an equivalent number of BSE cases based on a factor derived from UK data on reported BSE cases and amount of beef production.

We summed the country-specific numbers of reported BSE cases and the equivalent numbers of BSE cases that we estimated based on the amount of beef imported from the UK to calculate the total equivalent number of BSE cases for a country. We derived a ratio of BSE to vCJD from available BSE and vCJD data for nine countries (UK, Ireland, France, Portugal, Netherlands, Spain, KSA, Italy and Japan). We predicted the number of vCJD cases expected in a country based on the estimated total equivalent number of BSE cases and the BSE to vCJD ratio.

The prediction from the BSE model is in a good agreement with reported (attributed) vCJD cases for all countries except for KSA and Japan (see detailed results in Appendix A). The causes of discrepancy between BSE data and attributed vCJD cases for KSA and Japan are unknown. Any number of factors, such as imperfect surveillance systems for BSE and vCJD, inaccuracy of data on imports of UK beef, potential export of UK beef to a third country, or incorrect attribution of vCJD cases might potentially have led to the inconsistency. For example, the Japanese vCJD case was in an individual who paid a short visit to the UK—less than a month—during the period 1980-1996; however, the possibility that this individual acquired infection in the UK cannot be absolutely excluded.

Estimation of person-year exposure by travelers and immigrants

The overall risk contribution from each country depends not only on the vCJD case rate of the country but also the number of US donors who have traveled or resided (immigrants) in that county and therefore may have been exposed to the BSE agent. We incorporated outgoing US travel data and incoming immigration data to calculate potential person-years of exposure (PYE) of US donors in individual vCJD risk countries.

Major input data

Annual number of outbound travels from US: UN World Tourism Organization (58); International Trade Administration Office of Travel and Tourism Industries (ITA) (59)

Incoming immigration data: US Department of Homeland Security (DHS), Yearbook of Immigration Statistics (60)

Major assumptions

Average time spent on an international trip was 16 days based on ITA data; PYE for one trip was calculated as 16 days/365 days.

Immigrants from vCJD risk countries were those persons who came to the US after 1996 at the age of 17 years or older, had resided in their original country during the entire period 1980-1996, and had 17 years of full exposure. The PYE for each individual immigrant was adjusted based on the year and age when the individual moved to the US (see Appendix A for examples of adjustment).

PYE for travelers were calculated based on travel data for the period 1980-1996. For some countries, some risk may have remained after 1996. However, the BSE risk after 1996 was estimated to have been much smaller than the risk in 1996 and earlier. For simplicity, the model calculated PYE only through the year 1996 for all countries.

The model assumed that risk of exposure during the period 1980-1996 was evenly distributed, even though exposure risk for travels in different years during the risk period likely varied.

Risk ranking and vCJD risk contributions from individual countries

The vCJD risk contribution from an individual country was calculated by multiplying the country-specific vCJD case rate by the total PYE of US donors in that country, which was the sum of the PYE for travelers ($PYE_{Travelers}$) multiplying blood donation rate of US-

born citizens (DNR_{USborn}) and PYE for immigrants ($PYE_{Immigrants}$) multiplying the blood donation rate by immigrants ($DNR_{Immigrants}$). The calculations are summarized as the equation below:

Risk contribution =
vCJD case rate x ($PYE_{Travelers}$ x DNR_{USborn} + $PYE_{Immigrants}$ x $DNR_{Immigrants}$) (1)

We ranked countries by vCJD case rate, a rough indicator of individual risk in a vCJD risk country. As an effective policy, individual donors with the highest risk (travelers or immigrants who resided in the country with the highest vCJD case rate during the risk period) should be deferred first. As shown in Figure 2, we added the countries one by one to the list (vertical axis) starting with the country with the highest vCJD case rate. As every country was added to the list, we calculated and plotted the new cumulative risk (horizontal axis). The results of our vCJD risk contribution model indicated that 95% of total TTvCJD risk is contributed by donors exposed in three countries: the UK, Ireland and France. The percentage risk contribution by each individual country is listed in Table A-II-1in Appendix A. In these results, the total risk include the risk from all travelers and immigrants, even individuals who only spent 1 day in the specific risk country.

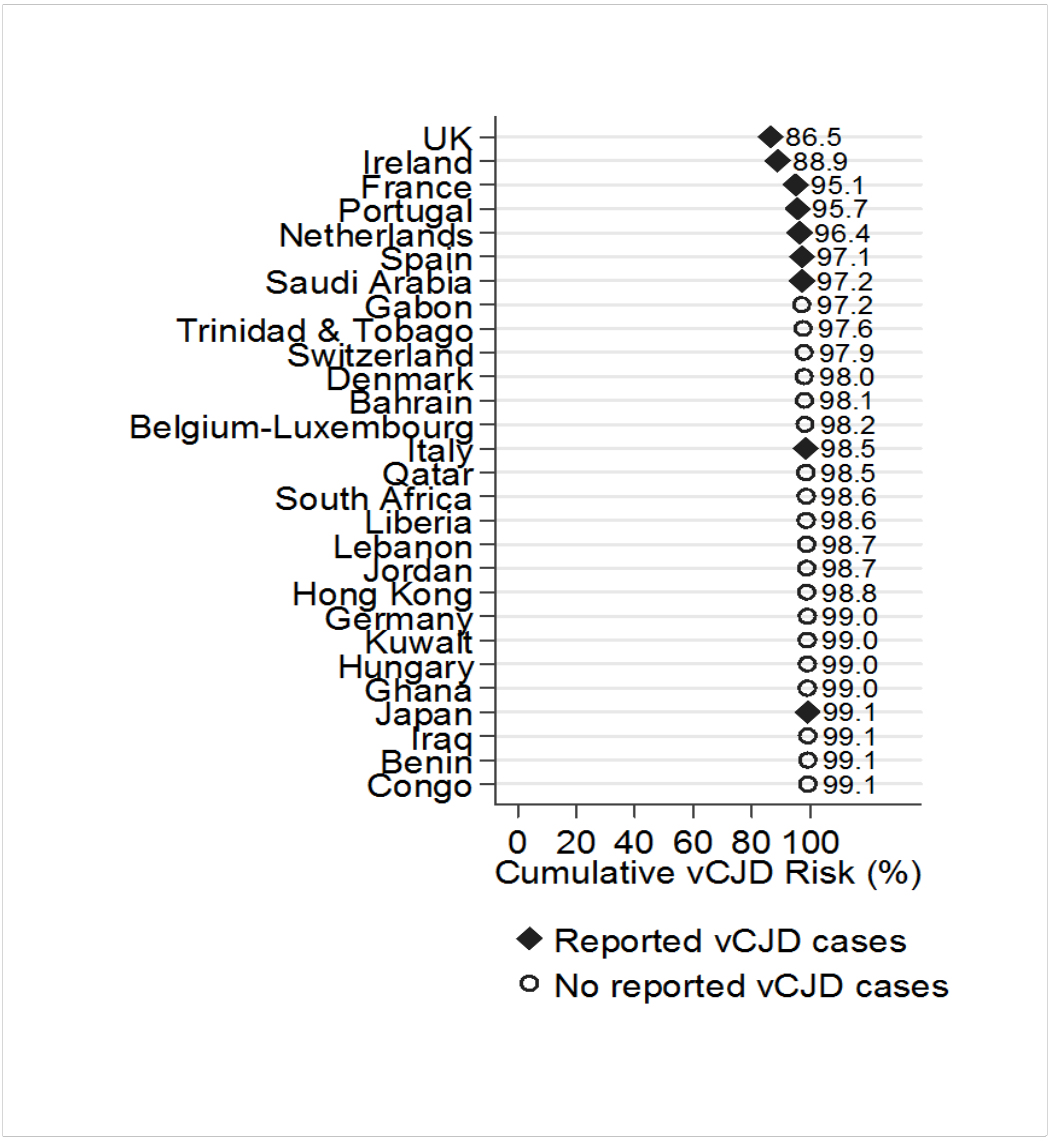

Figure 2. Cumulative risk contributions by countries. Countries with reported vCJD cases are marked with solid diamond markers. Countries with no reported vCJD cases are marked with hollow circles.

Evaluation of alternative donor deferral policies with risk mitigations

Evaluation of donor deferral options

Based on the results of FDA's vCJD global geographic risk assessment, FDA has proposed two alternative donor deferral options for evaluation by TSEAC:

Option 1. Current donor deferral policy (UK ≥3 months, 1980-1996; other countries in Europe ≥5 years, 1980-present)

Option 2. Modified donor deferral policy (UK ≥3 months, 1980-1996; France and Ireland: ≥5 years, 1980-2001)

The new option (***Option 2***) would eliminate donor deferrals for time donors spent in all countries except for the UK, France and Ireland, the three countries contributing approximately 95% of total vCJD risk. The risk reduction and donor loss for each of the two policy options were evaluated (see detailed calculations in Appendix A.)

Major input data

National Blood Donor Survey, 1999, ARC/REDS/ABC (61)

Major assumptions

The vCJD risk period was from 1980 to 1996 for UK (53). For France and Ireland, the risk period was from 1980 to 2001. The period of concern for deferrals stops after the end of 2001 because, by law, all EU countries, including France and Ireland, were to have implemented the same strong protective measures needed to prevent exposure of animals and humans to the BSE agent in feeds and food by that year (62).

The estimates of risk reduction and donor loss for the two donor deferral options are summarized in columns 2 and 5 of Table 3. Under current policy, the estimated TTvCJD risk has been reduced by 79% by donor deferral alone, and the blood system is estimated to have lost approximately 254,000 donors. Under Option 2, the model predicted a TTvCJD risk reduction of 78% by donor deferral alone, with an estimated gain of 100,000 donors when compared to current policy. Option 2 will remove 78% risk out of total 95% risk from UK, Ireland and France. However, some risk will remain because not all travelers and immigrants will be deferred.

B. Evaluation of effects of leukoreduction as an additional risk mitigation

We further evaluated the likely reduction in TTvCJD risk achieved by current voluntary LR (63) when added to the risk reduction from donor deferrals. Currently, approximately 95% of RBC units are thought to be voluntarily LR by blood collection agencies (64). Some added risk reduction might be achieved if all RBC products were LR. We estimated additional risk reduction through LR and total risk reduction combining donor

deferral and LR. The risk reduction was estimated for both the current 95% LR and for universal LR of RBC, if that was implemented.

In a previous FDA study, we developed a dose-response model for CJD (65) using nonhuman primate data (66). Our dose-response analysis estimated that LR would be expected to remove 54% of remaining vCJD risk (see detailed calculations in appendix). Analysis of those results suggests that the current 95% LR of RBC should reduce risk of TTvCJD by approximately 11% in addition to risk reduction through donor deferral. Universal LR (applying LR to the remaining 5% of RBC not currently processed) would reduce overall risk by an additional 0.6%. A total risk reduction of approximately 90% could be achieved by either of the two donor deferral options when combined with LR.

Table 3.
Model estimates of risk reduction and donor loss under different risk mitigation options

***Policy Options**	**Total percentage risk reduction (additional risk reduction)**			**Annual number of donors lost**
	Donor deferral only	**Donor deferral plus 95% LR**	**Donor deferral plus universal LR**	
Option 1	79.0%	89.8% (10.8%)	90.4% (0.6%)	254,091
Option 2	78.0%	89.3% (11.3%)	89.9% (0.6%)	156,021

*****Option 1. Current donor deferral policy (UK >3 months, 1980-1996; other countries in Europe >5 years, 1980-present); Option 2. Modified donor deferral policy (UK >3 months, 1980-1996; France & Ireland: >5 years, 1980-2001)

VI. Conclusions

Current geographic donor deferrals for vCJD risk combined with LR voluntarily implemented by blood centers have reduced risk of vCJD transmission via RBC by approximately 90%. The UK, Ireland and France are the three countries with the highest vCJD risks, together contributing approximately 95% total TTvCJD risk. FDA proposes a new donor deferral option (Option 2) that would maintain the donor deferrals for time spent in the UK, Ireland and France while relaxing deferrals for the remaining countries with relatively low vCJD risk. The risk assessment results suggest that risk of TTvCJD would not rise significantly should the new donor deferral option be implemented. By

deferring for time spent in just those three countries we might reduce risk by 78% (a reduction close to that afforded by current policies), even before considering the additional reduction in risk of TTvCJD from LR. The new donor deferral option would simplify the donor screening process and allow about 100,000 donors currently deferred to donate, while maintain a similar level of blood safety as that under current policy. The added reduction in risk of TTvCJD offered by universal LR is likely to be small.

V. Questions to the Committee

1) Please comment on and suggest any modifications to the structure of FDA's vCJD Geographic Risk Assessment Model for estimating the contribution of TTvCJD risk from donors exposed for various periods in different countries.

2) Please comment on and suggest any modifications to the assumptions (inputs) used in the FDA Model referenced in question 1.

3) Does the Committee agree that it is reasonable to move to revised geographic vCJD deferral as described in Option 2, Table 3 (UK >3 months, 1980-1996; France & Ireland: >5 years, 1980-2001)?

    a. If not, does the Committee agree that the deferral criteria should remain unchanged as described in Option 1, Table 3 (UK >3 months, 1980-1996; other countries in Europe >5 years, 1980-present)?

    b. Alternatively, please suggest and discuss other options that FDA should consider for geographically based donor deferrals.

4) Are there other vCJD risk mitigation strategies that FDA should consider at this time?

VI. References

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Appendix A

A-I. Attribution of vCJD cases based on history of residence for most likely exposure

Variant Creutzfeldt-Jakob disease (vCJD) has been reported in 12 countries (NCJDRSU, 2015). A total of 174 primary cases (food-borne) were reported in the U.K., and 27 were reported in France. The UK National CJD Research & Surveillance Unit (NCJDRSU) attributed seven primary cases reported outside the UK to the U.K., because the individuals associated with the cases had been spent more than six months in the UK during the vCJD risk period (1980-1996). NCJDRSU believed these individuals most likely acquired the disease in the UK (http://www.cjd.ed.ac.uk/documents/worldfigs.pdf). France, Ireland, Canada, and Taiwan, each reported one of these attributed cases. Ireland and the US, each reported two of these attributed cases. For a similar reason, the US Centers for Disease Control (CDC) attributed one American case to probable exposure in Kingdom of Saudi Arabia (KSA) (http://www.cdc.gov/ncidod/dvrd/vcjd/other/confirmed-case-in-texas.htm). A recently reported US vCJD case in an individual whose history of residence suggested that Kuwait, Lebanon and Russia were the most likely countries of exposure has not yet been included in FDA's analysis. The Public Health Agency of Canada (PHAC) attributed one case diagnosed in Canada to probable exposure in KSA (Coulthart, 2011).

A-II. vCJD case rate prediction based on BSE cases and UK beef importation

Only nine countries (Table A-II-1) have reported or assigned vCJD cases. For other countries we estimated vCJD case rate based on reported BSE and amount of beef imported from U.K.

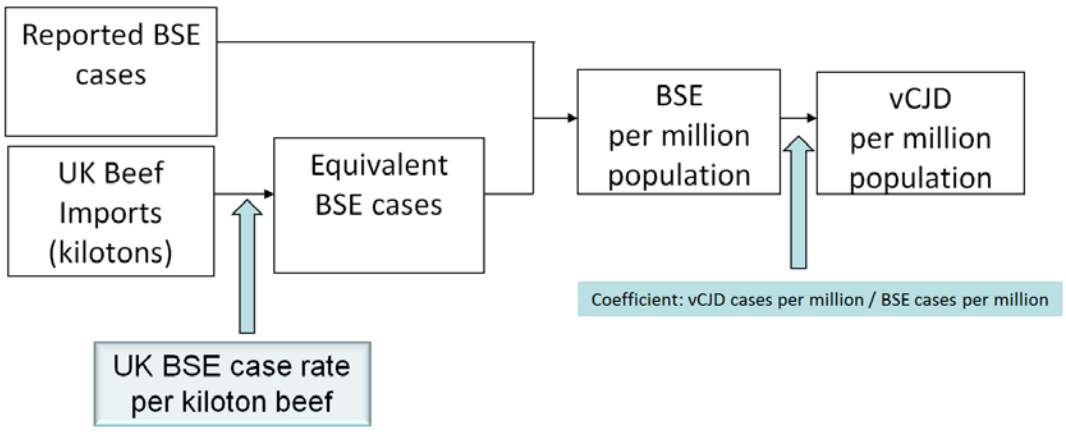

Figure A-II-1: Flow chart for model prediction of country specific vCJD case rate based on BSE exposure

Data:

1. Reported vCJD cases: NCJDRSU, http://www.cjd.ed.ac.uk/documents/worldfigs.pdf. For individuals resided in the UK for more than six months during the period 1980-1996, the cases are assigned to the UK, not to the reporting countries. One vCJD case reported in the US and one reported in Canada were attributed to KSA The fourth vCJD case in the US confirmed in May 2014 was not included in the analysis.
2. Reported BSE cases: World Organization of Animal Health, http://www.oie.int/?id=505
3. Amount of beef imported from UK: http://epp.eurostat.ec.europa.eu/newxtweb/ accessed on April 6, 2015. (Data available for years 1988 – 1996)
4. Country population data:
    a. United Nations: http://data.un.org/Data.aspx?d=POP&f=tableCode%3a1
    b. World Bank, http://data.worldbank.org/indicator/SP.POP.TOTL
5. Amount of beef consumption in U.K.: FAOSTAT, http://faostat3.fao.org/home/E

Rationales and assumptions:

1. Number of vCJD cases for each country is directly correlated with total BSE exposure of the population
2. Population may be exposed to the BSE infectious agent through two dietary sources: domestic beef or imported UK beef
3. Total BSE exposure in a specific country is represented by the sum of number of reported domestic BSE cases and equivalent number of BSE cases converted based on amount of imported UK beef.
4. Amount of UK beef exported during the period 1980-1987 (data not available) is assumed to be similar to the amounts exported during the period 1988-1996 (data available). The BSE risk from UK beef in the period 1980-1988 is expected to be much smaller than in the period 1988-1996 comparing the number of BSE cases reported in the UK in these two time periods. The impact of this assumption on the calculation of total risk from imported UK beef for each country is expected to be small.

Estimation of total BSE exposure risk

Total BSE exposure risk includes risk from two sources:

1. **Risk through consumption of beef from domestic and imported live cattle.** This part of the risk is measured by number of reported BSE cases (domestic plus

imported cattle) per million persons. To be conservative, even though no BSE cases were reported from 1980 to 1986, we assume a linear increasing trend of BSE cases between 1980 and 1987 to account for the potential risk from animals incubating the disease.

2. **Risk through consumption of imported UK beef during the period 1980-1996.** Data on UK beef importation are only available for years from 1988 to1996, and we applied the average annual amount of UK beef exported during period 1988 - 1996 to the period 1980 -1987.

The step by step calculations for estimation of total BSE exposure and predicted vCJD risk are described below.

Step 1: Convert the amount of beef imported from UK into equivalent number of BSE cases, so that two parts of risk are represented by the same metric. Because the BSE risk via UK beef varied by year during period 1980-1996, we calculated the equivalent BSE for UK beef importation in each individual year.

Average annual amount of beef production in UK 1980-1996

= Average annual amount of beef consumption in UK + Average annual amount of beef exportation from UK (1)

UK BSE rate per kiloton beef for individual years during period 1980-1996

= Annual numbers of reported BSE case in UK / Average annual amount of beef production in UK (2)

Equivalent BSE from imported UK beef in individual year

= Amount of imported UK beef in individual year in kiloton x UK BSE rate per kiloton beef for corresponding year (3)

Total Equivalent BSE from imported UK beef during period1980-1996

= Sum of Equivalent BSE from imported UK beef for period 1980-1996 (4)

Step 2: Estimate total equivalent BSE cases for each country by summing up country specific Equivalent Number of BSE from Imported UK Beef 1980-1996 and number of BSE cases reported by March 2015. Conservatively we use total number of BSE reported -to-date in this calculation; however, risk of vCJD might have been eliminated earlier in most of the countries through implementation of risk control measures to prevent BSE infectious agent from getting into human foods. Dividing the total equivalent BSE cases by population yields the imputed BSE case rate.

Prediction of vCJD risk

We plotted the reported vCJD case rate and imputed BSE case rate for nine countries with data on both vCJD and BSE (UK, Ireland, France, Portugal, Netherlands, Spain, KSA, Italy, Japan) in Figure A-II-2 to estimate the ratio of vCJD case rate to BSE case rate based on linear regression. The ratio derived was 1 vCJD case over 1000 BSE cases. The model fits the data well. However, we would like to point out that UK data have great influence on the coefficient estimate. We then estimated the vCJD case rate by dividing the imputed BSE case rate by a factor of 1000 for each country.

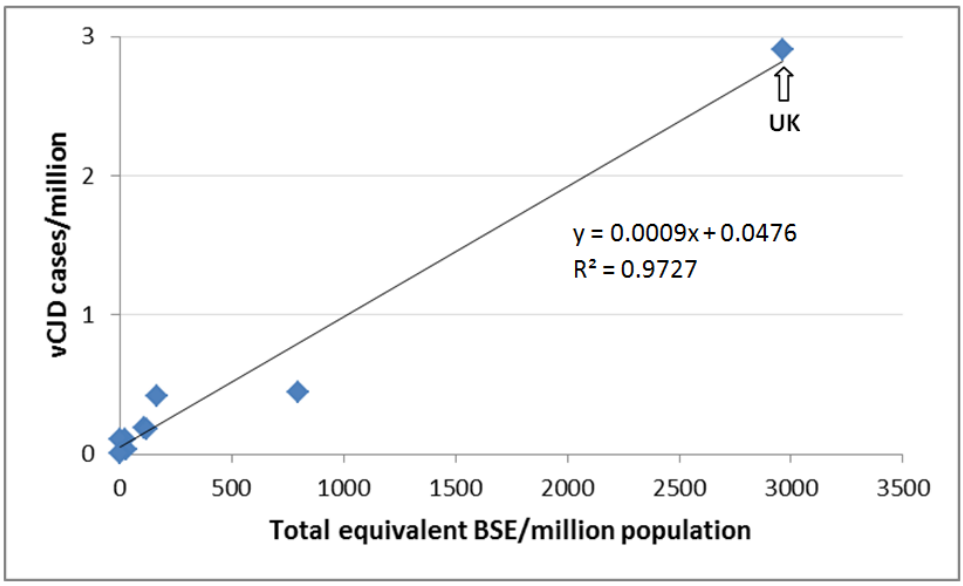

Figure A-II-2: Ratio of vCJD case rate to imputed BSE rate.

The prediction from the BSE model is in a good agreement with reported/attributed vCJD cases for all countries except for KSA and Japan (Table A-II-1). The causes of discrepancy between BSE data and attributed vCJD cases for KSA. and Japan are uncertain. Any number of factors, such as imperfect surveillance systems for BSE and vCJD, inaccuracy of data on imports of UK beef, potential export of UK beef to a third country, or incorrect attribution of vCJD cases might potentially have led to the inconsistency. For example, the Japanese vCJD case was an individual who paid a short visit to the UK—less than a month—during the period 1980-1996; however, the possibility that this individual acquired infection in the UK cannot be absolutely excluded.

Table A-II-1. Model prediction of number of vCJD cases based on BSE exposure compared with reported/attributed number of vCJD cases.

Country	Model predicted cases	Reported/attributed cases
UK	185	181
Ireland	3.6	2
France	10.6	26
Netherlands	2.0	3
Portugal	1.2	2
Italy	1.9	2
Spain	1.2	5
KSA	0.05	3
Japan	0.04	1
Any of other countries	<1	0

A-III. Estimation of person-year exposure by travelers and immigrants

We attributed vCJD risk to individual countries based on the vCJD case rate of the country and the number of US residents who have a history of travel or residence in the counties where they may have been exposed to the BSE agent. To combine the risk from travelers and immigrants, we converted exposure risk for both travelers and immigrants into person-year exposure (PYE).

Data:

1. Annual number of outbound travels from US:
   a. Yearbook of Tourism Statistics, 39th to 53rd editions, United Nations World Tourism Organization (UNWTO, 1986-2001) .
   b. International Trade Administration Office of Travel and Tourism Industries (ITA), http://travel.trade.gov/view/f-1999-11-001/index.html access on April 6, 2015.
2. Incoming immigration data: US Department of Homeland Security (DHS), the Yearbook of Immigration Statistics, http://www.dhs.gov/publications
3. Average number of nights (16 days) a US traveler spent overseas: ITA, http://travel.trade.gov/outreachpages/outbound_historical_statistics_analyses.html

Rationales and Assumptions:

1. Average time spent for an international trip is 16 days, PYE for one trip was calculated by 16 days/365 days

2. Immigrants from vCJD risk countries, who moved to US after 1996 at the age of 17 years or older, had resided in their original country during the entire period 1980-1996 and had 17 years of full exposure
3. Immigrants who moved to the US before 1996 had less than 17 years of exposure, e.g., an individual who moved to the US in 1990 (6 years before 1996) at the age 17 years has an 11-year exposure (17 years - 6 years= 11 years)
4. Immigrants who were born after 1980 had less than 17 years of exposure, e.g., an immigrant who was born in 1985 (5 years after 1980) and moved to the US after 1996 has an exposure period of 12 years (17 years-5 years= 12 years)

A-IV. Risk ranking and vCJD risk contributions from individual countries

Risk contributions from traveler and immigrants were calculated separately because of the different blood donation rates of the two groups. The risk contribution was calculated by multiplying the PYE (calculated in section A-III), blood donation rates (DNR) and model predicted vCJD case rate (CR). Total risk contribution from a country is the sum of the risk contribution from travelers and immigrants as described by equation below.

$$\text{Risk Contribution} = (PYE_{traveler} \times DNR_{US\ born} + PYE_{immigrant} \times DNR_{immigrant}) \times CR \quad (5)$$

Data:

Donation rates of US-born citizens and immigrants: NHIS data 1997-2010 estimated from the Integrated Health Interview Series (IHIS) database.

Minnesota Population Center and State Health Access Data Assistance Center, Integrated Health Interview Series: Version 5.0. Minneapolis: University of Minnesota, 2012. http://www.ihis.us

Rationales and Assumptions:

We applied donation rates of US-born citizens to travelers

The lists of countries and cumulative risk contribution are summarized in Table A-IV-1. The model results indicate that the UK, Ireland and France are top three countries with the highest vCJD case rate and together contribute approximately 95% of total vCJD risk.

Table A-IV-1: Cumulative risk contributions by countries. (Countries with reported or attributed vCJD cases are marked with *; countries without reported vCJD cases were ranked based on imputed vCJD case rate).

Country	vCJD Cases/Million population	Percentage risk contribution	Cumulative risk contribution
UK*	2.9053	86.47%	86.47%
Ireland*	0.4444	2.44%	88.91%
France*	0.4120	6.19%	95.10%
Portugal*	0.1887	0.57%	95.68%
Netherlands*	0.1796	0.76%	96.44%
Spain*	0.1085	0.61%	97.06%
KSA*	0.1060	0.10%	97.16%
Gabon	0.0961	0.004%	97.16%
Trinidad & Tobago	0.0611	0.38%	97.55%
Switzerland	0.0604	0.35%	97.90%
Denmark	0.0506	0.14%	98.04%
Bahrain	0.0461	0.01%	98.06%
Belgium-Luxembourg	0.0401	0.11%	98.17%
Italy*	0.0331	0.36%	98.53%
Qatar	0.0230	0.002%	98.54%
South Africa	0.0135	0.04%	98.58%
Liberia	0.0114	0.03%	98.61%
Lebanon	0.0114	0.05%	98.66%
Jordan	0.0107	0.04%	98.70%

Hong Kong	0.0104	0.10%	98.80%
Germany	0.0090	0.16%	98.96%
Kuwait	0.0089	0.01%	98.97%
Hungary	0.0085	0.02%	98.98%
Ghana	0.0082	0.04%	99.02%
Japan*	0.0080	0.08%	99.10%
Iraq	0.0066	0.03%	99.13%
Benin	0.0056	0.001%	99.13%
Congo	0.0050	0.002%	99.13%

A-V. Evaluation of donor deferral options

The balance between risk reduction and donor loss is an important consideration in developing donor deferral policy. Most travelers are only in the destination country for a short period of time and thus have low risk of BSE exposure. Donor deferral aiming at long-term travelers is an efficient approach to reduce vCJD risk while minimizing donor loss. We incorporated the cumulative time-spent in vCJD risk countries into donor deferral scenarios. We evaluated and calculated risk reduction and donor loss for two donor deferral options which indefinitely defer donors who have a history of cumulative time-spent in:

Option 1) UK: ≥3 months, 1980-1996;
France and other countries in Europe: ≥5 years, 1980- present (Current policy)

Option 2) UK: ≥3 months, 1980-1996;
France and Ireland: ≥5 years, 1980-2001

Data

1. National Blood Donor Travel Survey, 1999, ARC/REDS/ABC (TSEAC, 2000)
US blood donor age distribution. Data reported by countries to WHO Global Database on Blood Safety, 2008
http://www.who.int/worldblooddonorday/media/blood_donors_age_distribution_2011.pdf

The annual number of US blood donors (Department of Health and Human Services – 2011 National Blood Collection and Utilization Survey Report (NBCUS) http://www.hhs.gov/ash/bloodsafety/2011-nbcus.pdf

Rational and Assumptions

1. Risk period is from 1980 to 1996 for UK. The UK had implemented a range of precautionary food/feed-protective measures by 1996. Therefore, the BSE risk is considered to be negligible after 1996.
2. Risk is from 1980 to 2001 for Ireland and France because legislation in the European Union required implementation of similar measures by 2001 in all member states.
3. We applied the annual time-spent among donors during the period from 1980 to 1996 to derive the annual time-spent beyond 1996 by assuming same travel pattern.
4. National Blood Donor Travel Survey data (1999) provides data for time-spent in the UK and Ireland combined and in the rest of Europe combined. We used travel data from the World Tourism Organization (WTO) to adjust and derive the number of donors for each length of time-spent in the individual countries separately. The donor distribution by duration of stay in each country was assumed to be the same as that for UK However, WTO data has limitation because it does not distinguish between multiple individuals making single trips and a single individual making multiple trips.
5. We assumed 50% of donors who claimed their visits to U.K., Ireland, France, and the rest of Europe in the 1999 survey are no longer eligible to donate because of aging and adjusted the donor number accordingly.
   The risk reduction for each deferral option was determined based on the suggested deferral period for different countries under the option. The step by step calculations are described below:

   1. For each country, we calculated the relative risk compared to the UK, $RR_{country\ i}$, based on attributed/imputed vCJD case rate for that country (Case Rate $_{country\ i}$) and that for the UK (Case Rate $_{uk}$) using Equation 6 (For countries with attributed vCJD cases we used the number of attributed cases. For countries without attributed cases, we used the imputed vCJD case rate estimated by the BSE model described in A-II.):

      $$RR_{country\ i} = \text{Case Rate}_{country\ i} / \text{Case Rate}_{uk} \quad (6)$$

   2. For each country, the person-year exposure for donors in each time-spent duration group (PYE $_{country\ i,\ duration\ j}$) was determined by multiplying the total number of US donors, percentage donors in the group (Percent $_{country\ i,\ duration\ j}$), and the median travel duration for the group (Duration $_j$).

$$PYE_{\text{country i, duration j}} = \text{Total donor} \times \text{Percent}_{\text{country i, duration j}} \times \text{Duration}_{j} \quad (7)$$

3. The risk of donors for each duration group ($Risk_{\text{country i, duration j}}$) was determined by multiplying relative risk of destination country ($RR_{\text{country i}}$) and the person-year exposure for the group ($PYE_{\text{country i, duration j}}$).

$$Risk_{\text{country i, duration j}} = RR_{\text{country i}} \times PYE_{\text{country i, duration j}} \quad (8)$$

4. The risk reduction for each donor deferral scenario was calculated by summing up the risk from all donor groups who are to be deferred ($Risk_{\text{country i}^d, \text{duration j}^d}$, where the upper subscript d represents "deferred") under each scenario and dividing the sum by the total risk of all countries and duration groups.

$$\text{Risk Reduction} = \Sigma\, Risk_{\text{country i}^d, \text{duration j}^d} / \Sigma\, Risk_{\text{country i, duration j}} \quad (9)$$

5. The number of donors lost because of donor deferral for individual country was calculated by multiplying the cumulative percent of donors whose cumulative time-spent exceeded the deferral period ($Percent_{\text{country i}^d, \text{duration i}^d}$) by the total number of US donors.

$$\text{Donor Lost} = \text{Total donor} \times \Sigma\, Percent_{\text{country i}^d, \text{duration i}^d} \quad (10)$$

Under current policy, the estimated TTvCJD risk has been reduced by 79% by donor deferral alone, and the blood system is estimated to have lost approximately 254,000 donors every year. Under Option 2, the model predicted a TTvCJD risk reduction of 78% by donor deferral alone, with an estimated gain of 100,000 donors when compared to current policy. Donor deferral for UK accounts for 74.6% risk reduction and about 144,000 annual donor loss under both options. The model results are summarized in Table A-V-1.

Table A-V-1. Model estimates of risk reduction and donor loss for different donor deferral options

*Donor deferral options	Percentage risk reduction	Annual number donor lost
Option 1	**Total: 79.0%**	**Total: 254,091**
	UK (≥3 months): 74.6%	UK (≥3 months): 143,821
	France (≥5 years): 1.7%	France (≥5 years): 6,494
	Other countries in Europe (≥5 years): 2.7%	Other countries in Europe (≥5 years): 103,776
Option 2	**Total: 78.0%**	**Total: 156,021**
	UK (≥3 months): 74.6%	UK (≥3 months): 143,821
	Ireland(≥5 years): 1.7%	Ireland (≥5 years): 5,706
	France (≥5 years): 1.7%	France (≥5 years): 6,494

*Option 1. Current donor deferral policy (UK ≥3 months, 1980-1996; other countries in Europe ≥5 years, 1980-present); Option 2. Modified donor deferral policy (UK ≥3 months, 1980-1996; France & Ireland: ≥5 years, 1980-2001)

A-VI. Evaluation of Risk Mitigation by Leukoreduction

We further evaluated vCJD risk reduction should leukoreduction be applied as potential additional risk mitigation to each donor deferral options above. In a previous FDA study (Huang et al, 2014), we developed a dose-response model using data from nonhuman primates inoculated intracerebrally (i.c.) with brain tissues of patients with sporadic and familial CJD. We analyzed the data statistically using a beta-Poisson dose-response model described below:

$$P(d) = 1 - \left[1 + \left(\frac{d}{N_{50}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha} \qquad (11)$$

In Equation 11, d represents the infectious dose (milliliter of infected whole blood) and $P(d)$ represents the probability of acquiring TSE infection at dose d. Optimized values for parameters α and N_{50} are α=0.456 and N_{50} = 75. We can interpret the parameter N_{50} as the amount (in ml) of whole blood needed to cause a 50% chance of infection. In this case,

N_{50} equal to 75 means that 75 ml of infected blood will cause a 50% chance of infection. α is the slope parameter describing the host-pathogen interaction.

Either leukocytes or plasma contain about 50% of the infectious dose in whole blood (Gregori et al, 2004). The non-leukoreduced red blood cells (non-LR RBCs) are produced by removing plasma from whole blood. Typically, 30ml plasma remained (Roback JD, 2008), which contain about 6% of total infectious dose in whole blood (30 ml residual plasma out of total 250 ml plasma) . Summing infectious dose from leukocytes and residual plasma, the dose in non-LR RBCs was estimated to be 56% of the infectious dose of whole blood (50% plus 6%). The infectious dose in LR-RBCs is equivalent to 6% of that in whole blood (with most leukocytes removed).

Assuming one unit of blood is 450 ml, the model estimates an infection rate of 69.0% ("d=450ml ×56% = 252 ml" in Equation 11) and 31.4% ("d=450ml ×6% = 27 ml" in Equation 11) among recipients who receive one unit of non-LR RBCs and LR RBCs respectively (Figure A-VI-1). Therefore, leukoreduction reduces the total risk by 54% (1-31.4%/69.0% = 54%).

This factor (54%) was used to calculate the additional risk reduction with leukoreduction (additional risk Reduction $_{\text{LR-RBC}}$) using Equation 12 based on the remaining risk after donor deferral (remaining risk$_{\text{deferral}}$) and percentage LR-RBC (Percent $_{\text{LR-RBC}}$).

$$\text{Additional Risk Reduction}_{\text{LR-RBC}} = \text{remaining risk}_{\text{deferral}} \times \text{Percent}_{\text{LR-RBC}} \times 54\% \quad (12)$$

Currently, 95% of RBCs are leukoreduced (AABB Standards, 29th ed; FDA Guidance for Industry, *Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion*, 2012), so universal leukoreduction would only apply to the remaining 5% of RBCs. This would further reduce the risk of TTvCJD by approximately 0.6%.

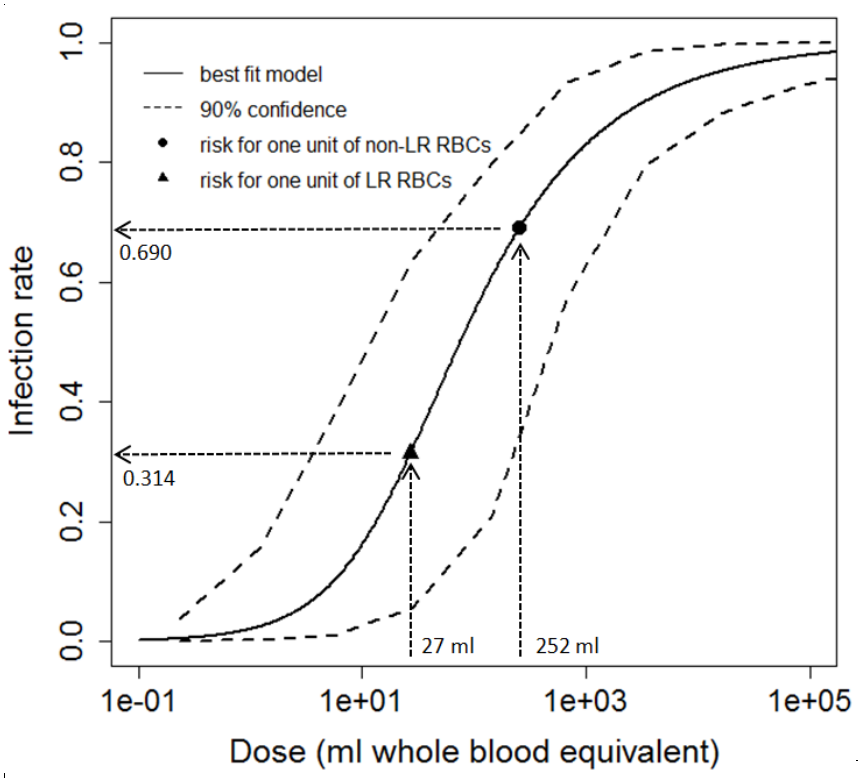

Figure A-VI -1: Beta-Poisson dose-response model for risk of transfusion-transmitted vCJD (Huang et al, 2014).

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Appendix B

Leukocyte Reduction of Blood Components: General Considerations

Consequences of leukocytes in transfused blood components

Despite effective fractionation processes, significant numbers of white blood cells remain in whole blood derived platelets and red blood cells. [1] Leukocytes release many potentially damaging proinflammatory and prothrombotic mediators during storage of blood components, such as IL-1, IL-6, TNF-α, and sCD40-L. [2 3 4 5] Adverse effects thought to be attributed to the effects of leukocytes in the transfused blood components include febrile nonhemolytic transfusion reactions (FNHTRs), graft-versus-host-disease (GVHD), transmission of blood-borne pathogens, alloimmunization, and immunomodulation. [6] Pre-storage leukocyte removal succeeds in eliminating a portion of such proinflammatory mediators. [7]

Leukoreduction has improved clinical care

The process of leukoreduction has improved clinical outcomes in Transfusion Medicine. The use of leukoreduced blood components has become standard of care for specific patient populations (including recipients of hematopoietic stem cell transplants, low birth weight neonates, pregnant patients), and several European nations as well as Canada have mandated universal leukocyte reduction for all transfusion recipients. [8] Established clinical benefits of leukoreduction include reductions in FNHTRs, [7] alloimmunization and subsequent platelet refractoriness, [9] and cytomegalovirus (CMV) transmission. [10]

Febrile nonhemolytic reactions

FNHTRs constitute one of the most common forms of acute transfusion reactions. FNHTRs are defined as an increase in core body temperature of 1°C or more during an allogeneic blood transfusion. Although frequently mild, the significance of such reactions manifests in their frequency, the burden of post-transfusion laboratory investigation and associated personnel/staffing resources, and delay in delivery of care.

FNHTR pathophysiology

Postulated pathophysiology of FNHTRs occurs by way of two potential mechanisms. First, passive transfer of donor inflammatory cytokines contributes to fever and other systemic symptoms. [12 37] Second, recipient antibodies recognize donor leukocytes, and the resulting complexes activate monocytes leading to pyrogenic sequelae. [11 13]

Reduction in FNHTRs - platelets

Heddle et al [7] compared plasma removal vs prestorage leukoreduction of platelets. They showed that there was a 9% absolute decrease in the frequency of acute reactions to platelets, characterized by fever, chills and/or rigors with plasma removal (21.3%) vs with prestorage leukoreduction (12.3%). Poststorage reduction does not eliminate febrile reactions to platelets as effectively as prestorage reduction, due to accumulation of cytokines from leukocytes during storage. [14 15 16 17] However, even prestorage leukoreduction fails to eliminate all FNHTRs. Residual reactions possibly occur due to accumulation of pyrogenic cytokines in donor units during the storage period. [18, 6] An additional speculation is that some residual reactions occur due to the presence of HLA antibodies to platelet membranes. [19]

Reduction in FNHTRs – Red Blood Cells (RBCs)

Significant levels of cytokines do not develop in stored RBCs. Therefore passively transferred donor cytokines do not cause febrile reactions to RBCs. Consequently, both prestorage and poststorage leukoreduction effectively mitigate febrile reactions to RBCs. Even filters less effective than those currently in practice (2nd generation as opposed to 4th generation) have been found effective at preventing febrile reactions to RBCs. [20]

HLA alloimmunization following transfusion

Patients who receive frequent platelet transfusions are especially prone to developing anti-HLA antibodies. The development of antibodies in this population often results in platelet refractoriness. It poses a particularly problematic scenario as this cohort of patients frequently comprises hematopoietic stem cell recipients in need of ongoing

platelet transfusion support, and development of alloantibodies can complicate or even prevent curative therapy.

HLA pathophysiology

The pathophysiology of HLA alloimmunization involves recognition of donor antigen-presenting cells (e.g. dendritic cells, monocytes) by recipient T-lymphocytes. Since the cohort of donor antigen-presenting cells is comprised of leukocytes, leukocyte reduction is hypothesized to mitigate such interactions. [47]

Leukoreduction decreases HLA alloimmunization

Multiple trials have shown decreased alloimmunization with transfusion of leukoreduced components. [21] [22] [23] [9] The TRAP study, a randomized control trial of 530 transfusion recipients assessed reduction in HLA alloimmunization. Patients with acute myelogenous leukemia (AML) who received leukoreduced blood components experienced significantly reduced rates of alloimmunization as compared to controls who received non-leukoreduced components (18% - pooled random donor platelets, 17% - filtered apheresis platelets, 45% - controls; $p < 0.001$).

Alloimmunization vs platelet refractoriness

However mitigation of platelet refractoriness does not directly equate with decreased alloimmunization and was seen in lesser measure in the majority of the above referenced studies. Whereas the rates of alloimmunization in the TRAP study were 45% in controls vs 17-18% in the leukoreduced arms, the rates of alloimmune platelet refractoriness were only 13% in controls versus 3 to 4% in the leukoreduced arms. Indeed, HLA alloantibody formation is only a surrogate marker of platelet refractoriness. [24] There are many additional contributing factors to platelet refractoriness including splenomegaly, disseminated intravascular dissemination (DIC), and sepsis. Additionally not all HLA antibodies mediate refractoriness.

CMV infection

CMV is a clinically important virus that presents with a range of symptoms, disproportionately affecting the immunosuppressed, in particular those with compromised cell-mediated immunity, and newborn populations. Congenital infection and infection in immunosuppressed adults can manifest with severe symptoms of fever, jaundice, pneumonitis, hepatosplenomegaly, thrombocytopenia, and leukopenia. Immunocompetent adults primarily experience fever and hepatitis. Blood transfusion is one of several routes by which CMV can be acquired.

Mechanism of CMV infection

CMV, a double stranded DNA virus, belongs to the family of human herpesviruses (HHV) and has a seroprevalence ranging from 40% - 100% depending on the geographic location and socio-economic status of the population. Asymptomatic seropositive individuals retain latent CMV infection in peripheral blood leukocytes. Accordingly, as CMV is highly cell-associated, transfusions of cellular blood components can result in the transmission of the virus.

CMV seronegative components

CMV seronegative cellular blood components have been a long-standing practice for preventing CMV transmission in high risk populations. [25] [26] However, CMV seronegative blood components have limitations. First, there is limited availability, due to the high CMV seroprevalence in the adult human population. Second, there is a significant concern that window-period donors will not be identified, due to recent acquisition (i.e. prior to seroconversion). Hence products that appear CMV seronegative may actually contain and transmit infectious virus. Therefore, efforts have focused on preventing CMV transmission in other ways, notably through the use of leukoreduced, or "CMV-reduced risk" products.

Leukoreduction decreases CMV transmission

Since CMV is highly cell-associated, leukoreduction can substantially reduce CMV transmission. Rates have been demonstrated to decrease from as much as 30% to ~1% in susceptible populations with the use of leukoreduced components. [27] [28] Several studies,

including a large randomized clinical trial found that seronegative and leukoreduced components did not pose significantly different risks of transfusion-transmitted-CMV. [10] However on secondary analysis, all six patients in the leukoreduced (filtered) arm developed CMV disease versus none of the patients in the seronegative arm, which was statistically significant ($p = 0.03$). Due to these findings, considerable controversy ensued and subsequently other studies have presented alternate evidence that leukoreduced products could actually pose a higher risk than CMV seronegative products. [29] While uncertainty remains regarding the optimal strategy for preventing CMV transmission, many hospitals provide leukoreduced cellular components as CMV-reduced risk without serologic testing, although there is considerable variability in practice. [26]

Additional potential benefits of leukoreduction

Although the effectiveness of leukoreduction versus seronegative components for transmission of CMV is uncertain, there are other benefits to leukoreduction. In addition to the accepted advantages, some evidence suggests additional gains, such as decreased post-operative infections [30] decreased TRALI (transfusion-related acute lung injury) and TACO (transfusion-associated circulatory overload) reactions. [31] Leukoreduction has the potential to decrease the transmission of other human herpes viruses, also associated with leukocytes. Transmission of HTLV, a white blood cell-associated virus, is also decreased by leukoreduction; a lookback study in England of cellular blood components confirmed as HTLV positive showed an odds ratio of 0.027 of testing HTLV positive after transfusion if the recipient had received a component that was leukoreduced compared to one that was not leukoreduced. [32] As discussed in the Issue Summary, ongoing laboratory and epidemiological research is being conducted to assess the potential of leukoreduction to mitigate transfusion transmitted vCJD; early results suggest that it is likely effective.

Controversial benefits

Controversy exists as to the effectiveness of leukoreduction in mitigating mortality, hospital length of stay, and overall hospital costs. [33] [34] A recent meta-analysis of randomized controlled trials did not find an association between mortality and transfusion of non-leukoreduced blood components. [35] A remaining question of debate is whether

WBC-containing allogeneic blood transfusion causes adverse transfusion-associated immunomodulation (TRIM) and whether leukoreduction would mitigate such effects. [36]

Limitations of leukoreduction

Accepted limitations of leukoreduction are its ineffectiveness in eliminating allergic reactions, [37] [17] preventing transmission of non-cell associated viruses, and preventing GVHD. Although data from the UK hemovigilance scheme Serious Hazards of Transfusion [38] does suggest a reduction in cases of TA-GVHD, in practice leukoreduction is not used as a method of prevention for this condition. [39] While leukoreduction does not damage the function of red cells or platelets, it does result in a loss of 15-25% of red cells and platelets. [40]

Methods of leukoreduction

Filtration is the most commonly used method to remove leukocytes from WBD blood components. Principles of leukocyte filtration are generally based on the larger size of leukocytes in relation to other cellular elements and their adherence to certain fiber types.[40] There are approximately 10^9 leukocytes in a donor unit of whole blood, compared to approximately 5×10^8 in a RBC unit. [19] Modern filters employ a combination of barrier filtration and cell adhesion, and are able to remove between 3-5 $\log_{10}$ (99.9-99.999%) of leukocytes. [40] Despite roughly equivalent degrees of leukocyte reduction achieved by different filters, the white blood cell subset composition of the product may vary. [41] Leukocyte reduction failures can be seen with red cells from donors with sickle trait, due to clogging of the filters. [42]

Pre-storage vs Post-storage leukoreduction

Prestorage leukoreduction has a failure rate of less than 1%. [8] Removal of leukocytes pre-storage is superior to post-storage removal for several reasons: first, it eliminates white cells before the release of damaging cytokines, second as it removes leukocytes before apoptosis it prevents contamination with membrane fragments, and third, it occurs in a controlled setting providing for better quality control and adherence to standards for leukocyte reduction. In addition, post-storage leukoreduction filters have been associated with acute hypotensive reactions, particularly in patients on ACE Inhibitors. [43] [44]

Process leukoreduction

Apheresis devices collect components having few residual leukocytes at the outset, obviating need for filtration, a procedure known as "process leukoreduction". [45] Apheresis devices collect leukoreduced components by in-line filtration or centrifugation, resulting in products most commonly with approximately 10^5 to 10^6 leukocytes per component.[45] All apheresis platelets collected in the US today are process leukoreduced. Approximately ninety-five percent of RBCs in the US are leukoreduced. [46]

Regulations

As per AABB Standards and the 2012 FDA Guidance for Industry on Pre-Storage Leukocyte Reduction, Leukoreduced RBCs and Apheresis Platelets should contain $<5 \times 10^6$ leukocytes per product. Whole blood derived platelets should contain $<8.3 \times 10^5$ leukocytes per product. At least 95% of units sampled must meet this criterion by validation and quality control (AABB Standards, 29th ed; FDA Guidance for Industry, *Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion*, 2012). Standards of the Council of Europe specify that less than 1×10^6 leukocytes should remain in a unit of leukoreduced RBC and less than 0.2×10^6 leukocytes in a unit of platelets prepared from whole blood. In practice, manufacturers claim that licensed leukoreduction filters eliminate even more leukocytes from components than required. [45 48 49 50]

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